Supplementary background information on Accelerated Approval Regulations and Orphan Drug Regulations

Subpart E of the Biologics Licensing Regulations:
Accelerated Approval of Biological Products for Serious or Life-Threatening Illnesses

§ 601.40 Scope.
This subpart applies to certain biological products that have been studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments (e.g., ability to treat patients unresponsive to, or intolerant of, available therapy, or improved patient response over available therapy).

§ 601.41 Approval based on a surrogate endpoint or on an effect on a clinical endpoint other than survival or irreversible morbidity.
FDA may grant marketing approval for a biological product on the basis of adequate and well-controlled clinical trials establishing that the biological product has an effect on a surrogate endpoint that is reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity. Approval under this section will be subject to the requirement that the applicant study the biological product further, to verify and describe its clinical benefit, where there is uncertainty as to the relation of the surrogate endpoint to clinical benefit, or of the observed clinical benefit to ultimate outcome. Postmarketing studies would usually be studies already underway. When required to be conducted, such studies must also be adequate and wellcontrolled. The applicant shall carry out any such studies with due diligence.

§ 601.43 Withdrawal procedures.
(a) For biological products approved under §§ 601.40 and 601.42, FDA may withdraw approval, following a hearing as provided in part 15 of this chapter, as modified by this section, if: (1) A postmarketing clinical study fails to verify clinical benefit; (2) The applicant fails to perform the required postmarketing study with due diligence; (3) Use after marketing demonstrates that postmarketing restrictions are inadequate to ensure safe use of the biological product; (4) The applicant fails to adhere to the postmarketing restrictions agreed upon; (5) The promotional materials are false or misleading; or (6) Other evidence demonstrates that the biological product is not shown to be safe or effective under its conditions of use. (b) Notice of opportunity for a hearing. The Director of the Center for Biologics Evaluation and Research will give the applicant notice of an opportunity for a hearing on the Center's proposal to withdraw the approval of an application approved under § 601.40 or § 601.41. The notice, which will ordinarily be a letter, will state generally the reasons for the action and the proposed grounds for the order. (c) Submission of data and information. (1) If the applicant fails to file a written request for a hearing within 15 days of receipt of the notice, the applicant waives the opportunity for a hearing. (2) If the applicant files

a timely request for a hearing, the agency will publish a notice of hearing in the FEDERAL REGISTER in accordance with §§ 12.32(e) and 15.20 of this chapter. (3) An applicant who requests a hearing under this section must, within 30 days of receipt of the notice of opportunity for a hearing, submit the data and information upon which the applicant intends to rely at the hearing. (d) *Separation of functions*. Separation of functions (as specified in § 10.55 of this chapter) will not apply at any point in withdrawal proceedings under this section. (e) *Procedures for hearings*. Hearings held under this section will be conducted in accordance with the provisions of part 15 of this chapter, with the following modifications: (1) An advisory committee duly constituted under part 14 of this chapter will be present at the hearing. The committee will be asked to review the issues involved and to provide advice and recommendations to the Commissioner of Food and Drugs. (2) The presiding officer, the advisory committee members, up to three representatives of the applicant, and up to three representatives of the Center may question any person during or at the conclusion of the person's presentation. No other person attending the hearing may question a person making a presentation. The presiding officer may, as a matter of discretion, permit questions to be submitted to the presiding officer for response by a person making a presentation. (f) *Judicial review*. The Commissioner's decision constitutes final agency action from which the applicant may petition for judicial review. Before requesting an order from a court for a stay of action pending review, an applicant must first submit a petition for a stay of action under § 10.35 of this chapter.

Orphan Drugs

In enacting the Orphan Drug Act in 1983, Congress sought to provide incentives to promote the development of drugs (including antibiotics and biological products) for the treatment of rare diseases. A drug may be considered for Orphan Designation if the drug is intended to treat a rare disease/condition affecting fewer than 200,000 people in the United States or if it is a vaccine, a preventive drug, or a diagnostic drug to be administered to less than 200,000 people per year in the United States. A drug may also be considered for Orphan Drug Designation if the drug has no expected profitability even if it treats a disease or condition affecting more than 200,000 people in the United States.

The incentives provided by the Orphan Drug Act for the innovator developing drugs with Orphan Designation are as follows:

The first sponsor to obtain Food and Drug Administration (FDA) marketing approval for a drug with Orphan Designation for the designated indication receives seven years of marketing exclusivity. No other sponsor may bring to market the "same drug" for the treatment of the same orphan indication for a period of seven years from the approval date.
The sponsor receives tax credits equal to 50% of the clinical investigation expenses.
The sponsor is exempt from Prescription Drug User Fee Act (PDUFA) fees.

The Orphan Drug Act does not address the criteria required for a drug with Orphan Designation to receive FDA marketing approval. A drug with Orphan Designation must meet the same criteria required to prove efficacy and safety as a drug without Orphan Designation. FDA review divisions may take into account the rare nature of the indications involved in Orphan Products when the number of patients to be studied is being considered.